Amendments to the Specification

Please replace the title with the following replacement title:

Keratinocyte Growth Factor-2 Polynucleotides

Please replace paragraph 10 on page 5 with the following replacement paragraph:

The present invention provides isolated nucleic acid molecules comprising a polynucleotide encoding the keratinocyte growth factor (KGF-2) having the amino acid sequence as shown in Figures 1A-1C [SEQ ID NO:2] or the amino acid sequence encoded by the cDNA clones deposited as ATCC® Deposit Number 75977 on December 16, 1994. The nucleotide sequence determined by sequencing the deposited KGF-2 clone, which is shown in Figures 1A-1C [SEQ ID NO:1], contains an open reading frame encoding a polypeptide of 208 amino acid residues, including an initiation codon at positions 1-3, with a predicted leader sequence of about 35 or 36 amino acid residues, and a deduced molecular weight of about 23.4 kDa. The amino acid sequence of the mature KGF-2 is shown in Figures 1A-1C, amino acid residues about 36 or 37 to 208 [SEQ ID NO:2].

Please replace paragraph 29 on page 9 with the following replacement paragraph:

Thus, one aspect of the invention provides an isolated nucleic acid molecule comprising a polynucleotide having a nucleotide sequence selected from the group consisting of: (a) a nucleotide sequence encoding the KGF-2 polypeptide having the complete amino acid sequence in Figures 1A-1C [SEQ ID NO:2]; (b) a nucleotide sequence encoding the mature KGF-2 polypeptide having the amino acid sequence at positions 36 or 37 to 208 in Figures 1A-1C [SEQ ID NO:2]; (c) a nucleotide sequence encoding the KGF-2 polypeptide having the complete amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No. 75977; (d) a nucleotide sequence encoding the mature KGF-2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No.75977; and (e) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c) or (d) above.

Please replace paragraph 31 on page 10 with the following replacement paragraph:

The invention further provides an isolated KGF-2 polypeptide having amino acid sequence selected from the group consisting of: (a) the amino acid sequence of the KGF-2 polypeptide having the complete 208 amino acid sequence, including the leader sequence shown in Figures 1A-1C [SEQ ID NO:2]; (b) the amino acid sequence of the mature KGF-2 polypeptide (without the leader) having the amino acid sequence at positions 36 or 37 to 208 in Figures 1A-1C [SEQ ID NO:2]; (c) the amino acid sequence of the KGF-2 polypeptide having the complete amino acid sequence, including the leader, encoded by the cDNA clone contained in ATCC® Deposit No.75977; and (d) the amino acid sequence of the mature KGF-2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No. 75977. The polypeptides of the present invention also include polypeptides having an amino acid sequence with at least 80% similarity, and more preferably at least 90%, 95%, 96%, 97%, 98% or 99% similarity to those described in (a), (b), (c) or (d) above, as well as polypeptides having an amino acid sequence at least 80% identical, more preferably at least 85% identical, and still more preferably 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to those above.

Please replace paragraph 39 on page 12 with the following replacement paragraph:

Figures 4A-4E show an analysis of the KGF-2 amino acid sequence. Alpha, beta, turn and coil regions; hydrophilicity and hydrophobicity; amphipathic regions; flexible regions; antigenic index and surface probability are shown. In the "Antigenic Index - Jameson-Wolf" graph, amino acid residues 41-109 in Figures 1A-1C [SEQ ID NO:2] correspond to the shown highly antigenic regions of the KGF-2 protein. Hydrophobic regions (Hopp-Woods Plot) fall below the median line (negative values) while hydrophilic regions (Kyte-Doolittle Plot) are found above the median line (positive values, e.g. amino acid residues 41-109). The plot is over the entire 208 amino acid ORF.

Please replace paragraph 96 on page 21 with the following replacement paragraph:

In accordance with an aspect of the present invention, there is provided an isolated nucleic acid (polynucleotide) which encodes for the polypeptide having the deduced amino acid sequence of Figures 1A-1C (SEQ ID NO:2) or for the polypeptide encoded by the cDNA of the clone deposited as ATCC® Deposit No. 75977 on December 16, 1994 at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA

20110-2209 or the polypeptide encoded by the cDNA of the clone deposited as ATCC® Deposit No. 75901 on September 29, 1994 at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.

Please replace paragraph 100 on page 23 with the following replacement paragraph:

Isolated nucleic acid molecules of the present invention include DNA molecules comprising an open reading frame (ORF) with an initiation codon at positions 1-3 of the nucleotide sequence shown in Figures 1A-1C (SEQ ID NO:1); DNA molecules comprising the coding sequence for the mature KGF-2 protein shown in Figures 1A-1C (last 172 or 173 amino acids) (SEQ ID NO:2); and DNA molecules which comprise a sequence substantially different from those described above but which, due to the degeneracy of the genetic code, still encode the KGF-2 protein. Of course, the genetic code is well known in the art. Thus, it would be routine for one skilled in the art to generate the degenerate variants described above.

Please replace paragraphs 103-104 on page 24 with the following replacement paragraphs:

The polynucleotide of the present invention may be in the form of RNA or in the form of DNA, which DNA includes cDNA, genomic DNA, and synthetic DNA. The DNA may be double-stranded or single-stranded, and if single stranded may be the coding strand or non-coding (anti-sense) strand. The coding sequence which encodes the mature polypeptide may be identical to the coding sequence shown in Figures 1A-1C (SEQ ID NO:1) or that of the deposited clone or may be a different coding sequence which coding sequence, as a result of the redundancy or degeneracy of the genetic code, encodes the same mature polypeptide as the DNA of Figures 1A-1C (SEQ ID NO:1) or the deposited cDNA.

The polynucleotide which encodes for the predicted mature polypeptide of Figures 1A-1C (SEQ ID NO:2) or for the predicted mature polypeptide encoded by the deposited cDNA may include: only the coding sequence for the mature polypeptide; the coding sequence for the mature polypeptide and additional coding sequence such as a leader or secretory sequence or a proprotein sequence; the coding sequence for the mature polypeptide (and optionally additional coding sequence) and non-coding sequence, such as intron or non-coding sequence 5' and/or 3' of the coding sequence for the predicted mature polypeptide. In

addition, a full length mRNA has been obtained which contains 5' and 3' untranslated regions of the gene (Figure 3 (SEQ ID NO:23)).

Please replace paragraphs 107-108 on page 25 with the following replacement paragraphs:

The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence of Figures 1A-1C (SEQ ID NO. 2) or the polypeptide encoded by the cDNA of the deposited clone. The variant of the polynucleotide may be a naturally occurring allelic variant of the polynucleotide or a nonnaturally occurring variant of the polynucleotide.

Thus, the present invention includes polynucleotides encoding the same predicted mature polypeptide as shown in Figures 1A-1C (SEQ ID NO:2) or the same predicted mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the polypeptide of Figures 1A-1C (SEQ ID NO:2) or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

Please replace paragraph 110 on page 26 with the following replacement paragraph:

As hereinabove indicated, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in Figures 1A-1C (SEQ ID NO:1) or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encode polypeptide.

Please replace paragraph 116 on page 27 with the following replacement paragraph:

Further embodiments of the invention include isolated nucleic acid molecules comprising a polynucleotide having a nucleotide sequence at least 80% identical, and more preferably at least 85%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to (a) a nucleotide sequence encoding the full-length KGF-2 polypeptide having the complete

amino acid sequence in Figures 1A-1C (SEQ ID NO:2), including the predicted leader sequence; (b) a nucleotide sequence encoding the mature KGF-2 polypeptide (full-length polypeptide with the leader removed) having the amino acid sequence at positions about 36 or 37 to 208 in Figures 1A-1C (SEQ ID NO:2); (c) a nucleotide sequence encoding the full-length KGF-2 polypeptide having the complete amino acid sequence including the leader encoded by the cDNA clone contained in ATCC® Deposit No. 75977; (d) a nucleotide sequence encoding the mature KGF-2 polypeptide having the amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No. 75977; (e) a nucleotide sequence encoding any of the KGF-2 analogs or deletion mutants described below; or (f) a nucleotide sequence complementary to any of the nucleotide sequences in (a), (b), (c),(d), or (e).

Please replace paragraph 118 on page 28 with the following replacement paragraph:

As a practical matter, whether any particular nucleic acid molecule is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to, for instance, the nucleotide sequence shown in Figures 1A-1C (SEQ ID NO:1) or to the nucleotides sequence of the deposited cDNA clone can be determined conventionally using known computer programs such as the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). Bestfit uses the local homology algorithm of Smith and Waterman, *Advances in Applied Mathematics 2*: 482-489 (1981), to find the best segment of homology between two sequences. When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference nucleotide sequence and that gaps in homology of up to 5% of the total number of nucleotides in the reference sequence are allowed.

Please replace paragraphs 122-123 on pages 30-31 with the following replacement paragraph:

The present application is directed to nucleic acid molecules at least 80%,85%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to the nucleic acid sequence shown in Figures 1A-1C [SEQ ID NO:1] or to the nucleic acid sequence of the deposited cDNA,

irrespective of whether they encode a polypeptide having KGF-2 activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having KGF-2 activity, one of skill in the art would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or a polymerase chain reaction (PCR) primer. Uses of the nucleic acid molecules of the present invention that do not encode a polypeptide having KGF-2 activity include, *inter alia,* (1) isolating the KGF-2 gene or allelic variants thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide precise chromosomal location of the KGF-2 gene, as described in Verma *et al., Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); and Northern Blot analysis for detecting KGF-2 mRNA expression in specific tissues.

Preferred, however, are nucleic acid molecules having sequences at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to the nucleic acid sequence shown in Figures 1A-1C [SEQ ID NO:1] or to the nucleic acid sequence of the deposited cDNA which do, in fact, encode a polypeptide having KGF-2 protein activity. By "a polypeptide having KGF-2 activity" is intended polypeptides exhibiting activity similar, but not necessarily identical, to an activity of the wild-type KGF-2 protein of the invention or an activity that is enhanced over that of the wild-type KGF-2 protein (either the full-length protein or, preferably, the mature protein), as measured in a particular biological assay.

Please replace paragraph 126 on page 32 with the following replacement paragraph:

Of course, due to the degeneracy of the genetic code, one of ordinary skill in the art will immediately recognize that a large number of the nucleic acid molecules having a sequence at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to the nucleic acid sequence of the deposited cDNA or the nucleic acid sequence shown in in Figures 1A-1C [SEQ ID NO:1] will encode a polypeptide "having KGF-2 protein activity." In fact, since degenerate variants of these nucleotide sequences all encode the same polypeptide, this will be clear to the skilled artisan even without performing the above described comparison assay. It will be further recognized in the art that, for such nucleic acid molecules that are not degenerate variants, a reasonable number will also encode a polypeptide having KGF-2 protein activity. This is because the skilled artisan is fully aware of amino acid substitutions that are either less likely or not likely to significantly effect protein function (e.g., replacing one aliphatic amino acid with a second aliphatic amino acid).

Please replace paragraph 128 on page 33 with the following replacement paragraph:

The present invention further relates to polynucleotides which hybridize to the hereinabove-described sequences if there is at least 70%, preferably at least 80%, and more preferably at least 85% and still more preferably 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identity between the sequences. The present invention particularly relates to polynucleotides which hybridize under stringent conditions to the hereinabove-described polynucleotides. As herein used, the term "stringent conditions" means hybridization will occur only if there is at least 95% and preferably at least 97% identity between the sequences. The polynucleotides which hybridize to the hereinabove described polynucleotides in a preferred embodiment encode polypeptides which either retain substantially the same biological function or activity as the mature polypeptide encoded by the cDNAs of Figures 1A-1C (SEQ ID NO:l) or the deposited cDNA(s).

Please replace paragraphs 132-134 on pages 34-35 with the following replacement paragraphs:

Of course, polynucleotides hybridizing to a larger portion of the reference polynucleotide (e.g., the deposited cDNA clone), for instance, a portion 50-750 nt in length, or even to the entire length of the reference polynucleotide, are also useful as probes according to the present invention, as are polynucleotides corresponding to most, if not all, of the nucleotide sequence of the deposited cDNA or the nucleotide sequence as shown in Figures 1A-1C [SEQ ID NO:1]. By a portion of a polynucleotide of "at least 20 nt in length," for example, is intended 20 or more contiguous nucleotides from the nucleotide sequence of the reference polynucleotide (e.g., the deposited cDNA or the nucleotide sequence as shown in Figures 1A-1C [SEQ ID NO:1]). As indicated, such portions are useful diagnostically either as a probe according to conventional DNA hybridization techniques or as primers for amplification of a target sequence by the polymerase chain reaction (PCR), as described, for instance, in Molecular Cloning, A Laboratory Manual, 2nd. edition, edited by Sambrook, J., Fritsch, E. F. and Maniatis, T., (1989), Cold Spring Harbor Laboratory Press, the entire disclosure of which is hereby incorporated herein by reference.

Since a KGF 2 cDNA clone has been deposited and its determined nucleotide sequence is provided in Figures 1A-1C [SEQ ID NO:1], generating polynucleotides which

hybridize to a portion of the KGF 2 cDNA molecule would be routine to the skilled artisan. For example, restriction endonuclease cleavage or shearing by sonication of the KGF 2 cDNA clone could easily be used to generate DNA portions of various sizes which are polynucleotides that hybridize to a portion of the KGF 2 cDNA molecule. Alternatively, the hybridizing polynucleotides of the present invention could be generated synthetically according to known techniques. Of course, a polynucleotide which hybridizes only to a poly A sequence (such as the 3' terminal poly(A) tract of the KGF 2 cDNA shown in Figures 1A-1C [SEQ ID NO:1]), or to a complementary stretch of T (or U) resides, would not be included in a polynucleotide of the invention used to hybridize to a portion of a nucleic acid of the invention, since such a polynucleotide would hybridize to any nucleic acid molecule containing a poly (A) stretch or the complement thereof (e.g., practically any double-stranded cDNA clone).

The invention further provides isolated nucleic acid molecules comprising a polynucleotide encoding an epitope-bearing portion of the KGF 2 protein. In particular, isolated nucleic acid molecules are provided encoding polypeptides comprising the following amino acid residues in Figures 1A-1C (SEQ ID NO:2), which the present inventors have determined are antigenic regions of the KGF 2 protein:

1. Gly41-Asn71: GQDMVSPEATNSSSSSFSSPSSAGRHVRSYN [SEQ ID NO:25];

2. Lys91-Ser109: KIEKNGKVSGTKKENCPYS [SEQ ID NO:26];

3. Asn135-Tyr164: NKKGKLYGSKEFNNDCKLKERIEENGYNTY [SEQ ID NO 27]; and

4. Asn181-Ala199: NGKGAPRRGQKTRRKNTSA [SEQ ID NO:28].

Also, there are two additional shorter predicted antigenic areas, Gln74-Arg78 of Figures 1A-1C (SEQ ID NO:2) and Gln170-Gln175 of Figure 1 (SEQ ID NO:2). Methods for generating such epitope-bearing portions of KGF 2 are described in detail below.

Please replace paragraph 136 on page 36 with the following replacement paragraph:

The present invention further relates to a polypeptide which has the deduced amino acid sequence of Figures 1A-1C (SEQ ID NO:2) or which has the amino acid sequence encoded by the deposited cDNA, as well as fragments, analogs and derivatives of such polypeptide.

Please replace paragraph 138 on page 37 with the following replacement paragraph:

The terms "fragment," "derivative" and "analog" when referring to the polypeptide, of Figures 1A-1C (SEQ ID NO:2) or that encoded by the deposited cDNA, means a polypeptide which retains essentially the same biological function or activity as such polypeptide. Thus, an analog includes a proprotein which can be activated by cleavage of the proprotein portion to produce an active mature polypeptide.

Please replace paragraph 140 on page 37 with the following replacement paragraph:

The fragment, derivative or analog of the polypeptide of Figures 1A-1C (SEQ ID NO:2) or that encoded by the deposited cDNA may be (i) one in which one or more of the amino acid residues are substituted with a conserved or non-conserved amino acid residue (preferably a conserved amino acid residue) and such substituted amino acid residue may or may not be one encoded by the genetic code, or (ii) one in which one or more of the amino acid residues includes a substituent group, or (iii) one in which the mature polypeptide is fused with another compound, such as a compound to increase the half-life of the polypeptide (for example, polyethylene glycol), or (iv) one in which the additional amino acids are fused to the mature polypeptide, such as a leader or secretory sequence or a sequence which is employed for purification of the mature polypeptide or a proprotein sequence. Such fragments, derivatives and analogs are deemed to be within the scope of those skilled in the art from the teachings herein.

Please replace paragraph 153 on page 40 with the following replacement paragraph:

As a practical matter, whether any particular polypeptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 97%, 98% or 99% identical to, for instance, the amino acid sequence shown in Figures 1A-1C [SEQ ID NO:2] or to the amino acid sequence encoded by deposited cDNA clone can be determined conventionally using known computer programs such the Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575 Science Drive, Madison, WI 53711). When using Bestfit or any other sequence alignment program to determine whether a particular sequence is, for instance, 95% identical to a reference sequence according to the present invention, the parameters are set, of course, such that the percentage of identity is calculated over the full length of the reference amino acid sequence and that gaps in

homology of up to 5% of the total number of amino acid residues in the reference sequence are allowed.

Please replace paragraph 162 on page 44 with the following replacement paragraph:

Non-limiting examples of antigenic polypeptides or peptides that can be used to generate KGF-2-specific antibodies include the following:

1. Gly41-Asn71: GQDMVSPEATNSSSSSFSSPSSAGRHVRSYN [SEQ ID NO:25];

2. Lys91-Ser109: KIEKNGKVSGTKKENCPYS [SEQ ID NO:26];

3. Asn135-Tyr164: NKKGKLYGSKEFNNDCKLKERIEENGYNTY [SEQ ID NO: 27]; and

4. Asn181-Ala199: NGKGAPRRGQKTRRKNTSA [SEQ ID NO:28].

Also, there are two additional shorter predicted antigenic areas, Gln74-Arg78 of Figures 1A-1C (SEQ ID NO:2) and Gln170-Gln175 of Figures 1A-1C (SEQ ID NO:2).

Please replace paragraph 164 on page 46 with the following replacement paragraph:

The present invention encompasses polypeptides comprising, or alternatively consisting of, an epitope of the polypeptide having an amino acid sequence of SEQ ID NO:2, or an epitope of the polypeptide sequence encoded by a polynucleotide sequence contained in ATCC® Deposit No. 75977 or encoded by a polynucleotide that hybridizes to the complement of the sequence of SEQ ID NO:1 or contained in ATCC® Deposit No. 75977 under stringent hybridization conditions or lower stringency hybridization conditions as defined *supra*. The present invention further encompasses polynucleotide sequences encoding an epitope of a polypeptide sequence of the invention (such as, for example, the sequence disclosed in SEQ ID NO:1) polynucleotide sequences of the complementary strand of a polynucleotide sequence encoding an epitope of the invention, and polynucleotide sequences which hybridize to the complementary strand under stringent hybridization conditions or lower stringency hybridization conditions defined *supra*.

Please replace paragraph 179 on page 53 with the following replacement paragraph:

Multimers of the invention may be the result of hydrophobic, hydrophilic, ionic and/or covalent associations and/or may be indirectly linked, by for example, liposome formation. Thus, in one embodiment, multimers of the invention, such as, for example, homodimers or homotrimers, are formed when polypeptides of the invention contact one another in solution.

In another embodiment, heteromultimers of the invention, such as, for example, heterotrimers or heterotetramers, are formed when polypeptides of the invention contact antibodies to the polypeptides of the invention (including antibodies to the heterologous polypeptide sequence in a fusion protein of the invention) in solution. In other embodiments, multimers of the invention are formed by covalent associations with and/or between the KGF-2 polypeptides of the invention. Such covalent associations may involve one or more amino acid residues contained in the polypeptide sequence (e.g., that recited in SEQ ID NO:2, or contained in the polypeptides encoded by the clone HPRCC57 or the clone contained in ATCC® Deposit No. 75977 or 75901). In one instance, the covalent associations are cross-linking between cysteine residues located within the polypeptide sequences which interact in the native (i.e., naturally occurring) polypeptide. In another instance, the covalent associations are the consequence of chemical or recombinant manipulation. Alternatively, such covalent associations may involve one or more amino acid residues contained in the heterologous polypeptide sequence in a KGF-2 fusion protein. In one example, covalent associations are between the heterologous sequence contained in a fusion protein of the invention (see, e.g., US Patent Number 5,478,925). In a specific example, the covalent associations are between the heterologous sequence contained in a KGF-2-Fc fusion protein of the invention (as described herein). In another specific example, covalent associations of fusion proteins of the invention are between heterologous polypeptide sequence from another protein that is capable of forming covalently associated multimers, such as for example, oseteoprotegerin (see, e.g., International Publication NO: WO 98/49305, the contents of which are herein incorporated by reference in its entirety). In another embodiment, two or more polypeptides of the invention are joined through peptide linkers. Examples include those peptide linkers described in U.S. Pat. No. 5,073,627 (hereby incorporated by reference). Proteins comprising multiple polypeptides of the invention separated by peptide linkers may be produced using conventional recombinant DNA technology.

Please replace paragraph 182 on page 55 with the following replacement paragraph:

In another example, proteins of the invention are associated by interactions between ~~Flag~~ FLAG® polypeptide sequence contained in fusion proteins of the invention containing ~~Flag~~ FLAG® polypeptide seuqence. In a further embodiment, associations proteins of the

invention are associated by interactions between heterologous polypeptide sequence contained in ~~Flag~~ FLAG® fusion proteins of the invention and anti-~~Flag~~ FLAG® antibody.

Please replace paragraph 185 on page 56 with the following replacement paragraph:

The present invention is further directed to fragments of the isolated nucleic acid molecules described herein. By a fragment of an isolated nucleic acid molecule having, for example, the nucleotide sequence of the deposited cDNA (clone HPRCC57), a nucleotide sequence encoding the polypeptide sequence encoded by the deposited cDNA, a nucleotide sequence encoding the polypeptide sequence depicted in Figures 1A-1C (SEQ ID NO:2), the nucleotide sequence shown in Figures 1A-1C (SEQ ID NO:1), or the complementary strand thereto, is intended fragments at least 15 nt, and more preferably at least about 20 nt, still more preferably at least 30 nt, and even more preferably, at least about 40, 50, 100, 150, 200, 250, 300, 325, 350, 375, 400, 450, 500, 550, or 600 nt in length. These fragments have numerous uses that include, but are not limited to, diagnostic probes and primers as discussed herein. Of course, larger fragments, such as those of 501-1500 nt in length are also useful according to the present invention as are fragments corresponding to most, if not all, of the nucleotide sequences of the deposited cDNA (clone HPRCC57) or as shown in Figures 1A-1C (SEQ ID NO:1). By a fragment at least 20 nt in length, for example, is intended fragments which include 20 or more contiguous bases from, for example, the nucleotide sequence of the deposited cDNA, or the nucleotide sequence as shown in Figures 1A-1C (SEQ ID NO:1).

Please replace paragraph 192 on page 59 with the following replacement paragraph:

The present invention is further directed to fragments of the KGF-2 polypeptide described herein. By a fragment of an isolated the KGF-2 polypeptide, for example, encoded by the deposited cDNA (clone HPRCC57), the polypeptide sequence encoded by the deposited cDNA, the polypeptide sequence depicted in Figures 1A-1C (SEQ ID NO:2), is intended to encompass polypeptide fragments contained in SEQ ID NO:2 or encoded by the cDNA contained in the deposited clone. Protein fragments may be "free-standing," or comprised within a larger polypeptide of which the fragment forms a part or region, most preferably as a single continuous region. Representative examples of polypeptide fragments of the invention, include, for example, fragments from about amino acid number 1-20, 21-40,

41-60, 61-80, 81-100, 102-120, 121-140, 141-160, 161-180, 181-200, 201-220, 221-240, 241-260, 261-280, or 281 to the end of the coding region. Moreover, polypeptide fragments can be at least 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, or 150 amino acids in length. In this context "about" includes the particularly recited ranges, larger or smaller by several (5, 4, 3, 2, or 1) amino acids, at either extreme or at both extremes.

Please replace paragraph 198 on page 62 with the following replacement paragraph:

Accordingly, the present invention further provides polypeptides having one or more residues deleted from the carboxy terminus of the amino acid sequence of the KGF-2 polypeptide shown in Figures 1A-1C (SEQ ID NO:2), as described by the general formula 1-n, where n is an integer from 2 to 207, where n corresponds to the position of amino acid residue identified in SEQ ID NO:2. More in particular, the invention provides polynucleotides encoding polypeptides comprising, or alternatively consisting of, the amino acid sequence of residues M-1 to H-207; M-1 to V-206; M-1 to V-205; M-1 to M-204; M-1 to P-203; M-1 to L-202; M-1 to F-201; M-1 to H-200; M-1 to A-199; M-1 to S-198; M-1 to T-197; M-1 to N-196; M-1 to K-195; M-1 to R-194; M-1 to R-193; M-1 to T-192; M-1 to K-191; M-1 to Q-190; M-1 to G-189; M-1 to R-188; M-1 to R-187; M-1 to P-186; M-1 to A-185; M-1 to G-184; M-1 to K-183; M-1 to G-182; M-1 to N-181; M-1 to L-180; M-1 to A-179; M-1 to V-178; M-1 to Y-177; M-1 to M-176; M-1 to Q-175; M-1 to R-174; M-1 to G-173; M-1 to N-172; M-1 to H-171; M-1 to Q-170; M-1 to W-169; M-1 to N-168; M-1 to F-167; M-1 to S-166; M-1 to A-165; M-1 to Y-164; M-1 to T-163; M-1 to N-162; M-1 to Y-161; M-1 to G-160; M-1 to N-159; M-1 to E-158; M-1 to E-157; M-1 to I-156; M-1 to R-155; M-1 to E-154; M-1 to K-153; M-1 to L-152; M-1 to K-151; M-1 to C-150; M-1 to D-149; M-1 to N-148; M-1 to N-147; M-1 to F-146; M-1 to E-145; M-1 to K-144; M-1 to S-143; M-1 to G-142; M-1 to Y-141; M-1 to L-140; M-1 to K-139; M-1 to G-138; M-1 to K-137; M-1 to K-136; M-1 to N-135; M-1 to M-134; M-1 to A-133; M-1 to L-132; M-1 to Y-131; M-1 to Y-130; M-1 to N-129; M-1 to S-128; M-1 to N-127; M-1 to I-126;M-1 to A-125; M-1 to K-124; M-1 to V-123; M-1 to A-122; M-1 to V-121; M-1 to V-120; M-1 to G-119; M-1 to I-118; M-1 to E-117; M-1 to V-116; M-1 to S-115; M-1 to T-114; M-1 to I-113; M-1 to E-112; M-1 to L-111; M-1 to I-110; M-1 to S-109; M-1 to Y-108; M-1 to P-107; M-1 to C-106; M-1 to N-105; M-1 to E-104; M-1 to K-103; M-1 to K-102; M-1 to T-101; M-1 to G-100; M-1 to S-99; M-1 to V-98; M-1 to K-97; M-1 to G-96; M-1 to N-95; M-1 to K-94; M-1 to E-93; M-1 to I-

92; M-1 to K-91; M-1 to L-90; M-1 to F-89; M-1 to Y-88; M-1 to K-87; M-1 to T-86; M-1 to F-85; M-1 to S-84; M-1 to F-83; M-1 to L-82; M-1 to K-81; M-1 to R-80; M-1 to W-79; M-1 to R-78; M-1 to V-77; M-1 to D-76; M-1 to G-75; M-1 to Q-74; M-1 to L-73; M-1 to H-72; M-1 to N-71; M-1 to Y-70; M-1 to S-69; M-1 to R-68; M-1 to V-67; M-1 to H-66; M-1 to R-65; M-1 to G-64; M-1 to A-63; M-1 to S-62; M-1 to S-61; M-1 to P-60; M-1 to S-59; M-1 to S-58; M-1 to F-57; M-1 to S-56; M-1 to S-55; M-1 to S-54; M-1 to S-53; M-1 to S-52; M-1 to N-51; M-1 to T-50; M-1 to A-49; M-1 to E-48; M-1 to P-47; M-1 to S-46; M-1 to V-45; M-1 to M-44; M-1 to D-43; M-1 to Q-42; M-1 to G-41; M-1 to L-40; M-1 to A-39; M-1 to Q-38; M-1 to C-37; M-1 to T-36; M-1 to V-35; M-1 to P-34; M-1 to V-33; M-1 to S-32; M-1 to S-31; M-1 to V-30; M-1 to L-29; M-1 to F-28; M-1 to L-27; M-1 to L-26; M-1 to L-25; M-1 to F-24; M-1 to C-23; M-1 to C-22; M-1 to C-21; M-1 to C-20; M-1 to C-19; M-1 to G-18; M-1 to P-17; M-1 to L-16; M-1 to H-15; M-1 to P-14; M-1 to F-13; M-1 to A-12; M-1 to S-11; M-1 to A-10; M-1 to C-9; M-1 to H-8; M-1 to T-7; of SEQ ID NO:2. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Please replace paragraph 202 on page 65 with the following replacement paragraph:

Also included are a nucleotide sequence encoding a polypeptide consisting of a portion of the complete KGF-2 amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No. 75977, where this portion excludes any integer of amino acid residues from 1 to about 198 amino acids from the amino terminus of the complete amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No. 75977, or any integer of amino acid residues from 1 to about 198 amino acids from the carboxy terminus, or any combination of the above amino terminal and carboxy terminal deletions, of the complete amino acid sequence encoded by the cDNA clone contained in ATCC® Deposit No. 75977. Polynucleotides encoding all of the above deletion mutant polypeptide forms also are provided.

Please replace paragraph 204 on page 66 with the following replacement paragraph:

Among the especially preferred fragments of the invention are fragments characterized by structural or functional attributes of KGF-2. Such fragments include amino acid residues that comprise alpha-helix and alpha-helix forming regions ("alpha-regions"), beta-sheet and beta-sheet-forming regions ("beta-regions"), turn and turn-forming regions

("turn-regions"), coil and coil-forming regions ("coil-regions"), hydrophilic regions, hydrophobic regions, alpha amphipathic regions, beta amphipathic regions, surface forming regions, and high antigenic index regions (i.e., containing four or more contiguous amino acids having an antigenic index of greater than or equal to 1.5, as identified using the default parameters of the Jameson-Wolf program) of complete (i.e., full-length) KGF-2 (SEQ ID NO:2). Certain preferred regions are those set out in Figure 4 and include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence depicted in Figures 1A-1C (SEQ ID NO:2), such preferred regions include; Garnier-Robson predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Chou-Fasman predicted alpha-regions, beta-regions, turn-regions, and coil-regions; Kyte-Doolittle predicted hydrophilic and hydrophobic regions; Eisenberg alpha and beta amphipathic regions; Emini surface-forming regions; and Jameson-Wolf high antigenic index regions, as predicted using the default parameters of these computer programs. Polynucleotides encoding these polypeptides are also encompassed by the invention.

Please replace paragraph 206 on page 67 with the following replacement paragraph:

The data representing the structural or functional attributes of KGF-2 set forth in Figures 1A-1C and/or Table I, as described above, was generated using the various modules and algorithms of the DNA*STAR set on default parameters. In a preferred embodiment, the data presented in columns VIII, IX, XIII, and XIV of Table I can be used to determine regions of KGF-2 which exhibit a high degree of potential for antigenicity. Regions of high antigenicity are determined from the data presented in columns VIII, IX, XIII, and/or IV by choosing values which represent regions of the polypeptide which are likely to be exposed on the surface of the polypeptide in an environment in which antigen recognition may occur in the process of initiation of an immune response.

Please replace paragraph 208 on page 67 with the following replacement paragraph:

The above-mentioned preferred regions set out in Figure 4 and in Table I include, but are not limited to, regions of the aforementioned types identified by analysis of the amino acid sequence set out in Figures 1A-1C. As set out in Figure 4 and in Table I, such preferred regions include Garnier-Robson alpha-regions, beta-regions, turn-regions, and coil-regions, Chou-Fasman alpha-regions, beta-regions, and coil-regions, Kyte-Doolittle hydrophilic

regions and hydrophobic regions, Eisenberg alpha- and beta-amphipathic regions, Karplus-Schulz flexible regions, Emini surface-forming regions and Jameson-Wolf regions of high antigenic index. The columns are labeled with the headings "Res", "Position", and Roman Numerals I-XIV. The column headings refer to the following features of the amino acid sequence presented in Figure 3, and Table I: "Res": amino acid residue of SEQ ID NO:2 and Figures 1A and 1B; "Position": position of the corresponding residue within SEQ ID NO:2 and Figures 1A and 1B; I: Alpha, Regions - Garnier-Robson; II: Alpha, Regions - Chou-Fasman; III: Beta, Regions - Garnier-Robson; IV: Beta, Regions - Chou-Fasman; V: Turn, Regions - Garnier-Robson; VI: Turn, Regions - Chou-Fasman; VII: Coil, Regions - Garnier-Robson; VIII: Hydrophilicity Plot - Kyte-Doolittle; IX: Hydrophobicity Plot - Hopp-Woods; X: Alpha, Amphipathic Regions - Eisenberg; XI: Beta, Amphipathic Regions - Eisenberg; XII: Flexible Regions - Karplus-Schulz; XIII: Antigenic Index - Jameson-Wolf; and XIV: Surface Probability Plot - Emini.

Please replace paragraph2 224-232 on pages 83-88 with the following replacement paragraph:

Particularly preferred KGF 2 polypeptides are shown below (numbering starts with the first amino acid in the protein (Met) (Figures 1A-1C (SEQ ID NO:2)):

Thr (residue 36) -- Ser (residue 208)

Cys (37) -- Ser (208)

Gln (38) -- Ser (208)

Ala (39) -- Ser (208)

Leu (40) -- Ser (208)

Gly (41) -- Ser (208)

Gln (42) -- Ser (208)

Asp (43) -- Ser (208)

Met (44) -- Ser (208)

Val (45) -- Ser (208)

Ser (46) -- Ser (208)

Pro (47) -- Ser (208)

Glu (48) -- Ser (208)

Ala (49) -- (Ser (208)

Thr (50) -- Ser (208)

Asn (51) -- Ser (208)

Ser (52) -- Ser (208)

Ser (53) -- Ser (208)

Ser (54) -- Ser (208)

Ser (55) -- Ser (208)

Ser (56) -- Ser (208)

Phe (57) -- Ser (208)

Ser (59) -- Ser (208)

Ser(62) -- Ser (208)

Ala(63) -- Ser (208)

Gly (64) -- Ser (208)

Arg (65) -- Ser (208)

Val (67) -- Ser (208)

Ser (69) -- Ser (208)

Val (77) -- Ser (208)

Arg (80) -- Ser (208)

Met(1), Thr (36), or Cys (37) -- His (207)

Met (1), Thr (36), or Cys (37) -- Val (206)

Met (1), Thr (36), or Cys (37) -- Val (205)

Met(1), Thr (36), or Cys (37) Met (204)

Met(1), Thr (36), or Cys (37) -- Pro (203)

Met(1), Thr (36), or Cys(37) -- Leu (202)

Met(1), Thr (36), or Cys (37) -- Phe (201)

Met(1), Thr (36), or Cys (37) -- His (200)

Met(1), Thr (36), or Cys (37) -- Ala (199)

Met (1), Thr (36), or Cys (37) -- Ser (198)

Met (1), Thr (36), or Cys (37) -- Thr (197)

Met(1), Thr (36), or Cys (37) -- Asn (196)

Met(1), Thr (36), or Cys (37) -- Lys (195)

Met (1), Thr (36), or Cys (37) -- Arg (194)

Met(1), Thr (36), or Cys (37) -- Arg (193)

Met(1), Thr (36), or Cys (37) -- Thr (192)

Met(1), Thr (36), or Cys (37) -- Lys (191)

Met(1), Thr (36), or Cys (37) -- Arg (188)

Met(1), Thr (36), or Cys (37) -- Arg (187)

Met(1), Thr (36), or Cys (37) -- Lys (183)

Preferred embodiments include the N-terminal deletions Ala (63) -- Ser (208) (KGF 2Δ28) (SEQ ID NO:68) and Ser (69) -- Ser (208) (KGF 2Δ33) (SEQ ID NO:96). Other preferred N-terminal and C-terminal deletion mutants are described in Examples 13 and 16 (c) of the specification and include: Ala (39) -- Ser (208) (SEQ ID NO:116); Pro (47) -- Ser (208) of Figures 1A-1C (SEQ ID NO:2); Val (77) -- Ser (208) (SEQ ID NO:70); Glu (93) -- Ser (208) (SEQ ID NO:72); Glu (104) -- Ser (208) (SEQ ID NO:74); Val (123) - Ser (208) (SEQ ID NO:76); and Gly (138) -- Ser (208) (SEQ ID NO:78). Other preferred C-terminal deletion mutants include: Met (1), Thr (36), or Cys (37) -- Lys (153) of Figures 1A-1C (SEQ ID NO:2).

Also included by the present invention are deletion mutants having amino acids deleted from both the -- terminus and the C-terminus. Such mutants include all combinations of the N-terminal deletion mutants and C-terminal deletion mutants described above, e.g., Ala (39) His (200) of Figures 1A-1C (SEQ ID NO:2), Met (44) Arg (193) of Figure 1 (SEQ ID NO:2), Ala (63) -- Lys (153) of Figures 1A-1C (SEQ ID NO:2), Ser (69) - Lys (153) of Figures 1A-1C (SEQ ID NO:2), etc. etc. etc . . . . Those combinations can be made using recombinant techniques known to those skilled in the art.

Thus, in one aspect, N-terminal deletion mutants are provided by the present invention. Such mutants include those comprising the amino acid sequence shown in Figures 1A-1C (SEQ ID NO:2) except for a deletion of at least the first 38 N-terminal amino acid residues (i.e., a deletion of at least Met (1) -- Gln (38)) but not more than the first 147 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 38 N-terminal amino acid residues (i.e., a deletion of at least Met (1) -- Gln (38)) but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 46 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 62 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues

of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 68 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 76 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 92 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 103 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the first 122 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2).

In addition to the ranges of N-terminal deletion mutants described above, the present invention is also directed to all combinations of the above described ranges, e.g., deletions of at least the first 62 N-terminal amino acid residues but not more than the first 68 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 62 N-terminal amino acid residues but not more than the first 76 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 62 N-terminal amino acid residues but not more than the first 92 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 62 N-terminal amino acid residues but not more than the first 103 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 68 N-terminal amino acid residues but not more than the first 76 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 68 N-terminal amino acid residues but not more than the first 92 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 68 N-terminal amino acid residues but not more than the first 103 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 46 N-terminal amino acid residues but not more than the first 62 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 46 N-terminal amino acid residues but not more than the first 68 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the first 46 N-terminal amino acid residues but not more than the first 76 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); etc. etc. etc. . . .

In another aspect, C-terminal deletion mutants are provided by the present invention. Preferably, the N-terminal amino acid residue of said C-terminal deletion mutants is amino acid residue 1 (Met), 36 (Thr), or 37 (Cys) of Figures 1A-1C (SEQ ID NO:2). Such mutants include those comprising the amino acid sequence shown in Figures 1A-1C (SEQ ID NO:2) except for a deletion of at least the last C-terminal amino acid residue (Ser (208)) but not more than the last 55 C-terminal amino acid residues (i.e., a deletion of amino acid residues Glu (154) - Ser (208)) of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the last C-terminal amino acid residue but not more than the last 65 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the last 10 C-terminal amino acid residues but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2).

Alternatively, the deletion will include at least the last 20 C-terminal amino acid residues but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the last 30 C-terminal amino acid residues but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the last 40 C-terminal amino acid residues but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, the deletion will include at least the last 50 C-terminal amino acid residues but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2).

In addition to the ranges of C-terminal deletion mutants described above, the present invention is also directed to all combinations of the above described ranges, e.g., deletions of at least the last C-terminal amino acid residue but not more than the last 10 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the last C-terminal amino acid residue but not more than the last 20 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the last C-terminal amino acid residue but not more than the last 30 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the last C-terminal amino acid residue but not more than the last 40 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the last 10 C-terminal amino acid residues but not more than the last 20 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the last 10 C-terminal amino acid residues but not more than the last 30 C-terminal amino acid residues of Figures 1A-1C

(SEQ ID NO:2); deletions of at least the last 10 C-terminal amino acid residues but not more than the last 40 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); deletions of at least the last 20 C-terminal amino acid residues but not more than the last 30 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2); etc. etc. etc. . . .

In yet another aspect, also included by the present invention are deletion mutants having amino acids deleted from both the – terminal and C-terminal residues. Such mutants include all combinations of the N-terminal deletion mutants and C-terminal deletion mutants described above. Such mutants include those comprising the amino acid sequence shown in Figures 1A-1C (SEQ ID NO:2) except for a deletion of at least the first 46 N-terminal amino acid residues but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2) and a deletion of at least the last C-terminal amino acid residue but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Alternatively, a deletion can include at least the first 62, 68, 76, 92, 103, or 122 N-terminal amino acids but not more than the first 137 N-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2) and a deletion of at least the last 10, 20, 30, 40, or 50 C-terminal amino acid residues but not more than the last 55 C-terminal amino acid residues of Figures 1A-1C (SEQ ID NO:2). Further included are all combinations of the above described ranges.

Please replace paragraph 235 on page 89 with the following replacement paragraph:

A further embodiment of the invention relates to a polypeptide which comprises the amino acid sequence of a KGF-2 polypeptide having an amino acid sequence which contains at least one amino acid substitution, but not more than 50 amino acid substitutions, even more preferably, not more than 40 amino acid substitutions, still more preferably, not more than 30 amino acid substitutions, and still even more preferably, not more than 20 amino acid substitutions. Of course, in order of ever-increasing preference, it is highly preferable for a peptide or polypeptide to have an amino acid sequence which comprises the amino acid sequence of a KGF-2 polypeptide, which contains at least one, but not more than 20, 19, 18, 17, 16, 15, 14, 13, 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2 or 1 amino acid substitutions. In specific embodiments, the number of additions, substitutions, and/or deletions in the amino acid sequence of Figures 1A-1C or fragments thereof (e.g., the mature form and/or other fragments described herein), is 1-5, 5-10, 5-25, 5-50, 10-50 or 50-150, conservative amino acid substitutions are preferable.

Please replace paragraph 237 on page 91 with the following replacement paragraph:

By the designation, for example, Ala (49) Gln is intended that the Ala at position 49 of Figures 1A-1C (SEQ ID NO:2) is replaced by Gln.

Please replace paragraph 255 on page 106 with the following replacement paragraph:

As demonstrated in Figure 4A-4E, there are 4 major highly hydrophilic regions in the KGF-2 protein. Amino acid residues Gly41 - Asn 71, Lys91 - Ser 109, Asn135 - Tyr 164 and Asn 181 - Ala 199 [SEQ ID NOS:25-28]. There are two additional shorter predicted antigenic areas, Gln 74 - Arg 78 of Figure 1 (SEQ ID NO:2) and Gln 170 - Gln 175 of Figures 1A-1C (SEQ ID NO:2). Hydrophilic parts are known to be mainly at the outside (surface) of proteins and, therefore, available for antibodies recognizing these regions. Those regions are also likely to be involved in the binding of KGF-2 to its receptor(s). Synthetic peptides derived from these areas can interfere with the binding of KGF-2 to its receptor(s) and, therefore, block the function of the protein. Synthetic peptides from hydrophilic parts of the protein may also be agonistic, i.e. mimic the function of KGF-2.

Please replace paragraph 265 on page 111 with the following replacement paragraph:

As one of skill in the art will appreciate, and as discussed above, the polypeptides of the present invention comprising an immunogenic or antigenic epitope can be fused to other polypeptide sequences. For example, the polypeptides of the present invention may be fused with the constant domain of immunoglobulins (IgA, IgE, IgG, IgM), or portions thereof (CH1, CH2, CH3, or any combination thereof and portions thereof) resulting in chimeric polypeptides. Such fusion proteins may facilitate purification and may increase half-life *in vivo*. This has been shown for chimeric proteins consisting of the first two domains of the human CD4-polypeptide and various domains of the constant regions of the heavy or light chains of mammalian immunoglobulins. See, e.g., EP 394,827; Traunecker *et al.*, *Nature, 331*:84-86 (1988). Enhanced delivery of an antigen across the epithelial barrier to the immune system has been demonstrated for antigens (e.g., insulin) conjugated to an FcRn binding partner such as IgG or Fc fragments (see, e.g., PCT Publications WO 96/22024 and WO 99/04813). IgG Fusion proteins that have a disulfide-linked dimeric structure due to the IgG portion disulfide bonds have also been found to be more efficient in binding and

neutralizing other molecules than monomeric polypeptides or fragments thereof alone. *See, e.g.*, Fountoulakis *et al.*, *J. Biochem.*, *270*:3958-3964 (1995). Nucleic acids encoding the above epitopes can also be recombined with a gene of interest as an epitope tag (e.g., the hemagglutinin ("HA") tag or ~~flag~~ FLAG® tag) to aid in detection and purification of the expressed polypeptide. For example, a system described by Janknecht *et al.* allows for the ready purification of non-denatured fusion proteins expressed in human cell lines (Janknecht *et al.*, *1991, Proc. Natl. Acad. Sci. USA 88*:8972- 897). In this system, the gene of interest is subcloned into a vaccinia recombination plasmid such that the open reading frame of the gene is translationally fused to an amino-terminal tag consisting of six histidine residues. The tag serves as a matrix binding domain for the fusion protein. Extracts from cells infected with the recombinant vaccinia virus are loaded onto Ni^{2+} nitriloacetic acid-agarose column and histidine-tagged proteins can be selectively eluted with imidazole-containing buffers.

Please replace paragraph 295 on page 125 with the following replacement paragraph:

Methods for producing and screening for specific antibodies using hybridoma technology are routine and well known in the art and are discussed in detail in the Examples. In a non-limiting example, mice can be immunized with a polypeptide of the invention or a cell expressing such peptide. Once an immune response is detected, e.g., antibodies specific for the antigen are detected in the mouse serum, the mouse spleen is harvested and splenocytes isolated. The splenocytes are then fused by well known techniques to any suitable myeloma cells, for example cells from cell line SP20 available from the ATCC®. Hybridomas are selected and cloned by limited dilution. The hybridoma clones are then assayed by methods known in the art for cells that secrete antibodies capable of binding a polypeptide of the invention. Ascites fluid, which generally contains high levels of antibodies, can be generated by immunizing mice with positive hybridoma clones.

Please replace paragraph 331 on page 143 with the following replacement paragraph:

Moreover, the antibodies or fragments thereof of the present invention can be fused to marker sequences, such as a peptide to facilitate purification. In preferred embodiments, the marker amino acid sequence is a hexa-histidine peptide, such as the tag provided in a pQE vector (QIAGEN, Inc., 9259 Eton Avenue, Chatsworth, CA, 91311), among others, many of which are commercially available. As described in Gentz *et al.*, *Proc. Natl. Acad. Sci. USA*

86:821-824 (1989), for instance, hexa-histidine provides for convenient purification of the fusion protein. Other peptide tags useful for purification include, but are not limited to, the "HA" tag, which corresponds to an epitope derived from the influenza hemagglutinin protein (Wilson *et al.*, *Cell 37*:767 (1984)) and the "~~flag~~ FLAG®" tag.

Please replace paragraph 353 on page 151 with the following replacement paragraph:

As indicated, the expression vectors will preferably include at least one selectable marker. Such markers include dihydrofolate reductase, G418 or neomycin resistance for eukaryotic cell culture and tetracycline, kanamycin or ampicillin resistance genes for culturing in *E. coli* and other bacteria. Representative examples of appropriate hosts include, but are not limited to, bacterial cells, such as *E. coli*, *Streptomyces* and *Salmonella typhimurium* cells; fungal cells, such as yeast cells (e.g., *Saccharomyces cerevisiae* or *Pichia pastoris* (ATCC® Accession No. 201178)); insect cells such as *Drosophila* S2 and *Spodoptera* Sf9 cells; animal cells such as CHO, COS, 293, and Bowes melanoma cells; adenoviruses and plant cells. Appropriate culture mediums and conditions for the above-described host cells are known in the art.

Please replace paragraph 361 on page 153 with the following replacement paragraph:

Thus, the present invention is also directed to expression vector useful for the production of the proteins of the present invention. This aspect of the invention is exemplified by the pHE4-5 vector (SEQ ID NO:147). The pHE4-5 vector containing a cDNA insert encoding KGF-2 Δ33 was deposited at the ATCC® on January 9, 1998 as ATCC® No. 209575.

Please replace paragraph 374 on page 157 with the following replacement paragraph:

As a representative but nonlimiting example, useful expression vectors for bacterial use can comprise a selectable marker and bacterial origin of replication derived from commercially available plasmids comprising genetic elements of the well known cloning vector pBR322 (ATCC® 37017). Such commercial vectors include, for example, pKK223-3 (Pharmacia Fine Chemicals, Uppsala, Sweden) and GEM1 (Promega Biotec, Madison, WI, USA). These pBR322 "backbone" sections are combined with an appropriate promoter and the structural sequence to be expressed.

Please replace paragraph 746 on page 291 with the following replacement paragraph:

The DNA sequence encoding KGF-2, ATCC® # 75977, is initially amplified using PCR oligonucleotide primers corresponding to the 5' and 3' end sequences of the processed KGF-2 cDNA (including the signal peptide sequence). The 5' oligonucleotide primer has the sequence:

5' CCCCACATGTGGAAATGGATACTGACACATTGTGCC 3' (SEQ ID No. 3) contains an Afl III restriction enzyme site including and followed by 30 nucleotides of KGF-2 coding sequence starting from the presumed initiation codon. The 3' sequence:

5' CCCAAGCTTCCACAAACGTTGCCTTCCTCTATGAG 3' (SEQ ID No. 4) contains complementary sequences to Hind III site and is followed by 26 nucleotides of KGF-2. The restriction enzyme sites are compatible with the restriction enzyme sites on the bacterial expression vector pQE-60 (Qiagen, Inc. Chatsworth, CA). pQE-60 encodes antibiotic resistance (Amp^r) , a bacterial origin of replication (ori), an IPTG-regulatable promoter operator (P/0), a ribosome binding site (RBS) , a 6-His tag and restriction enzyme sites. pQE-60 is then digested with NcoI and HindIII. The amplified sequences are ligated into pQE-60 and are inserted in frame. The ligation mixture is then used to transform *E. coli* strain M15/rep 4 (Qiagen, Inc.) by the procedure described in Sambrook, J., *et al., Molecular Cloning: A Laboratory Manual*, Cold Spring Laboratory Press, (1989). M15/rep4 contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kan^r) . Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis. Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml) . The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 ($O.D._{600}$) of between 0.4 and 0.6. IPTG ("Isopropyl-B-D-thiogalacto pyranoside") is then added to a final concentration of 1 mM. IPTG interacts with the lacI repressor to cause it to dissociate from the operator, forcing the promoter to direct transcription. Cells are grown an extra 3 to 4 hours. Cells are then harvested by centrifugation. The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl. After clarification, solubilized KGF-2 is purified from this solution by chromatography on a Heparin affinity column under conditions that allow for tight binding of

the proteins (Hochuli, E., *et al., J. Chromatography 411*:177-184 (1984)). KGF-2 (75% pure) is eluted from the column by high salt buffer.

Please replace paragraph 747 on page 292 with the following replacement paragraph:

The DNA sequence encoding KGF 2, ATCC® # 75977, is initially amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the truncated version of the KGF 2 polypeptide. The truncated version comprises the polypeptide minus the 36 amino acid signal sequence, with a methionine and alanine residue being added just before the cysteine residue which comprises amino acid 37 of the full-length protein. The 5' oligonucleotide primer has the sequence
5' CATGCCATGGCGTGCCAAGCCCTTGGTCAGGACATG 3' (SEQ ID NO:5) contains an NcoI restriction enzyme site including and followed by 24 nucleotides of KGF 2 coding sequence. The 3' sequence 5' CCCAAGCTTCCACAAACGTTGC CTTCCTC TATGAG 3' (SEQ ID NO:6) contains complementary sequences to Hind III site and is followed by 26 nucleotides of the KGF 2 gene. The restriction enzyme sites are compatible with the restriction enzyme sites on the bacterial expression vector pQE-60 (Qiagen, Inc., Chatsworth, CA). pQE-60 encodes antibiotic resistance (Ampr) , a bacterial origin of replication (ori), an IPTG-regulatable promoter operator (P/0), a ribosome binding site (RBS) , a 6-His tag and restriction enzyme sites. pQE-60 is then digested with NcoI and HindIII. The amplified sequences are ligated into pQE-60 and are inserted in frame. The ligation mixture is then used to transform E. coli strain M15/rep 4 (Qiagen, Inc.) by the procedure described in Sambrook, J., et al., Molecular Cloning: A Laboratory Manual, Cold Spring Laboratory Press, (1989). M15/rep4 contains multiple copies of the plasmid pREP4, which expresses the lacI repressor and also confers kanamycin resistance (Kanr). Transformants are identified by their ability to grow on LB plates and ampicillin/kanamycin resistant colonies are selected. Plasmid DNA is isolated and confirmed by restriction analysis. Clones containing the desired constructs are grown overnight (O/N) in liquid culture in LB media supplemented with both Amp (100 ug/ml) and Kan (25 ug/ml). The O/N culture is used to inoculate a large culture at a ratio of 1:100 to 1:250. The cells are grown to an optical density 600 (O.D.600) of between 0.4 and 0.6. IPTG ("Isopropyl-B-D-thiogalacto pyranoside") is then added to a final concentration of 1 mM. IPTG induces by inactivating the laci repressor, clearing the P/O leading to increased gene expression. Cells are grown an extra 3 to 4 hours. Cells are then

harvested by centrifugation. The cell pellet is solubilized in the chaotropic agent 6 Molar Guanidine HCl. After clarification, solubilized KGF 2 is purified from this solution by chromatography on a Heparin affinity column under conditions that allow for tight binding the proteins (Hochuli, E. et al., J. Chromatography 411:177-184 (1984)). KGF 2 protein is eluted from the column by high salt buffer.

Please replace paragraph 748 on page 294 with the following replacement paragraph:

The DNA sequence encoding the full length KGF-2 protein, ATCC® # 75977, is amplified using PCR oligonucleotide primers corresponding to the 5' and 3' sequences of the gene:

Please replace paragraph 755 on page 295 with the following replacement paragraph:

1 µg of BaculoGold™ virus DNA and 5 µg of the plasmid pBacKGF 2 are mixed in a sterile well of a microtiter plate containing 50 µl of serum free Grace's medium (Life Technologies Inc., Gaithersburg, MD). Afterwards 10 µl Lipofectin plus 90 µl Grace's medium are added, mixed and incubated for 15 minutes at room temperature. Then the transfection mixture is added drop-wise to the Sf9 insect cells (ATCC® CRL 1711) seeded in a 35 mm tissue culture plate with 1 ml Grace's medium without serum. The plate is rocked back and forth to mix the newly added solution. The plate is then incubated for 5 hours at 27°C. After 5 hours the transfection solution is removed from the plate and 1 ml of Grace's insect medium supplemented with 10% fetal calf serum is added. The plate is put back into an incubator and cultivation continued at 27°C for four days.

Please replace paragraph 760 on page 297 with the following replacement paragraph:

A typical mammalian expression vector contains the promoter element, which mediates the initiation of transcription of mRNA, the protein coding sequence, and signals required for the termination of transcription and polyadenylation of the transcript. Additional elements include enhancers, Kozak sequences and intervening sequences flanked by donor and acceptor sites for RNA splicing. Highly efficient transcription can be achieved with the early and late promoters from SV40, the long terminal repeats (LTRs) from Retroviruses, e.g., RSV, HTLVI, HIVI and the immediate early promoter of the cytomegalovirus (CMV). However, cellular signals can also be used (e.g., human actin promoter). Suitable expression

vectors for use in practicing the present invention include, for example, vectors such as pSVL and pMSG (Pharmacia, Uppsala, Sweden), pRSVcat (ATCC® 37152), pSV2dhfr (ATCC® 37146) and pBC12MI (ATCC® 67109). Mammalian host cells that could be used include, human Hela, 283, H9 and Jurkart cells, mouse NIH3T3 and C127 cells, Cos 1, Cos 7 and CV1, African green monkey cells, quail QC1-3 cells, 293T cells, mouse L cells and Chinese hamster ovary cells.

Please replace paragraph 766 on page 299 with the following replacement paragraph:

The DNA sequence encoding KGF 2, ATCC® # 75977, is constructed by PCR using two primers: the 5' primer

5' TAACGAGGATCCGCCATCATGTGGAAATGGATACTGACAC 3' (SEQ ID NO:9) contains a BamHI site followed by 22 nucleotides of KGF 2 coding sequence starting from the initiation codon; the 3' sequence

5' TAAGCACTCGAGTGAGTGTACCACCATTGGAAGAAATG 3' (SEQ ID NO:10) contains complementary sequences to an XhoI site, HA tag and the last 26 nucleotides of the KGF 2 coding sequence (not including the stop codon). Therefore, the PCR product contains a BamHI site, KGF 2 coding sequence followed by an XhoI site, an HA tag fused in frame, and a translation termination stop codon next to the HA tag. The PCR amplified DNA fragment and the vector, pcDNA-3'HA, are digested with BamHI and XhoI restriction enzyme and ligated resulting in pcDNA-3'HA-KGF 2. The ligation mixture is transformed into E. coli strain XL1 Blue (Stratagene Cloning Systems, La Jolla, CA) the transformed culture is plated on ampicillin media plates and resistant colonies are selected. Plasmid DNA was isolated from transformants and examined by PCR and restriction analysis for the presence of the correct fragment. For expression of the recombinant KGF 2, COS cells were transfected with the expression vector by DEAE-DEXTRAN method (Sambrook, J., et al., Molecular Cloning: A Laboratory Manual, Cold Spring Laboratory Press, (1989)). The expression of the KGF 2 HA protein was detected by radiolabelling and immunoprecipitation method (Harlow, E. & Lane, D., Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory Press, (1988)). Cells were labelled for 8 hours with 35S-cysteine two days post transfection. Culture media were then collected and cells were lysed with detergent (RIPA buffer (150 mM NaCl, 1% NP-40, 0.1% SDS, 1% NP-40, 0.5% DOC, 5OmM Tris, pH 7.5) (Wilson, I., et al., Id. 37:767 (1984)). Both cell lysate and culture media

were precipitated with a HA specific monoclonal antibody. Proteins precipitated were analyzed on 15% SDS-PAGE gels.

Please replace paragraph 767 on page 300 with the following replacement paragraph:

The vector pC1 is used for the expression of KFG-2 protein. Plasmid pC1 is a derivative of the plasmid pSV2-dhfr [ATCC® Accession No. 37146]. Both plasmids contain the mouse DHFR gene under control of the SV40 early promoter. Chinese hamster ovary- or other cells lacking dihydrofolate activity that are transfected with these plasmids can be selected by growing the cells in a selective medium (alpha minus MEM, Life Technologies) supplemented with the chemotherapeutic agent methotrexate. The amplification of the DHFR genes in cells resistant to methotrexate (MTX) has been well documented (see, e.g., Alt, F.W., Kellems, R.M., Bertino, J.R., and Schimke, R.T., 1978, *J. Biol. Chem. 253*:1357-1370, Hamlin, J.L. and Ma, C. 1990, *Biochem. et Biophys. Acta, 1097*:107-143, Page, M.J. and Sydenham, M.A. 1991, *Biotechnology Vol. 9*:64-68). Cells grown in increasing concentrations of MTX develop resistance to the drug by overproducing the target enzyme, DHFR, as a result of amplification of the DHFR gene. If a second gene is linked to the DHFR gene it is usually co-amplified and over-expressed. It is state of the art to develop cell lines carrying more than 1,000 copies of the genes. Subsequently, when the methotrexate is withdrawn, cell lines contain the amplified gene integrated into the chromosome(s).

Please replace paragraphs 771-773 on page 301 with the following replacement paragraph:

The DNA sequence encoding KFG-2, ATCC® No. 75977, is amplified using PCR oligonucleotide primers corresponding to the 5′ and 3′ sequences of the gene:

The 5′ primer has the sequence:

5'TAACGAGGATCCGCCATCATGTGGAA ATGGATACTGACAC 3' (SEQ ID NO:9) containing the underlined BamH1 restriction enzyme site followed by 21 bases of the sequence of KGF-2 of Figures 1A-1C (SEQ ID NO:1). Inserted into an expression vector, as described below, the 5′ end of the amplified fragment encoding human KGF-2 provides an efficient signal peptide. An efficient signal for initiation of translation in eukaryotic cells, as described by Kozak, M., J. Mol. Biol. 196:947-950 (1987) is appropriately located in the vector portion of the construct.

The 3′ primer has the sequence:

5' TAAGCAGGATCCTGAGTGTA CCACCATTGGAAGAAATG 3' (SEQ ID NO:10) containing the BamH1 restriction followed by nucleotides complementary to the last 26 nucleotides of the KGF-2 coding sequence set out in Figures 1A-1C (SEQ ID NO:1), not including the stop codon.

Please replace paragraph 857 on page 325 with the following replacement paragraphs:

The results revealed that KGF-2 protein (Thr (36) - Ser (208) of Figures 1A-1C (SEQ ID NO:2) with a N-terminal Met added thereto) strongly stimulated the proliferation of Baf3 cells expressing the KGF receptor, FGFR2iiib isoform, as indicated by ^{3}H-thymidine incorporation (Figure 22A). Interestingly, a slight stimulatory effect of KGF-2 on the proliferation of Baf3 cells expressing the FGFR1iiib isoform was observed. KGF-2 did not have any effects on cells expressing the FGFR3iiib or the FGFR4 forms of the receptor.

Please replace paragraph 928 on page 347 with the following replacement paragraphs:

Groups of four lewis rats (190~210gm) were injected subcutaneously in the foot pad of the right hind paw with 120µl solution containing 2.5 nMol of PAF, together with the following reagents: 125 µg of Ckb-10(B5), 24 µg of LPS, 73 µg of KGF-2 (Thr (36) - Ser (208) of Figures 1A-1C (SEQ ID NO:2) with a N-terminal Met) or no protein. The left hind paws were given the same amount of buffer to use as parallel control. Paw volume was quantified immediately before, or 30 and 90 minutes after PAF injection using a plethysmograph system. Percent (%) change of paw volume were calculated.

Please replace paragraphs 1111-1112 on page 405 with the following replacement paragraphs:

An appropriate construct for KGF-2 gene therapy delivery is pVGI.0-KGF-2. This construct contains the full native open reading frame of KGF-2 cloned into the expression vector pVGI.0. pVGI.0 contains a kanamycin resistance gene, a CMV enhancer, and an RSV promoter. pVGI.0-KGF-2 was deposited at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209, on June 30, 1999, and given ATCC® Deposit No. PTA290. This construct was made by subcloning the KGF-2 ORF from a previously sequence verified KGF-2 construct into the expression vector pVGI-0, using methods well known in the art.

Another appropriate construct for KGF-2 delivery is pVGI-0-MPIFspKGF2Δ33. This construct contains the native sequence of KGF-2 Δ 33 fused to the MPIF (CK_ 8) heterologous signal peptide cloned into the expression vector pVGI-0. pVGI.0-MPIFspKGF2Δ33 was deposited at the American Type Culture Collection Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209, on June 30, 1999, and given ATCC® Deposit No. PTA289. This construct was made using methods well known in the art and the following primers:

Please replace paragraph 1161 on page 419 with the following replacement paragraph:

A plasmid comprising a cDNA having the nucleotide sequence of SEQ ID NO:173 was deposited as ATCC® Deposit No. PTA-2183 on July 3, 2000, at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.

Please replace paragraph 1164 on page 420 with the following replacement paragraph:

A plasmid comprising a cDNA having the nucleotide sequence of SEQ ID NO:176 was deposited as ATCC® Deposit No. PTA-2184 on July 3, 2000, at the American Type Culture Collection, Patent Depository, 10801 University Boulevard, Manassas, VA 20110-2209.